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HOW DO APOLIPOPROTEINS ApoB AND ApoA-I PERFORM IN PATIENTS WITH ACUTE CORONARY SYNDROMES

KOLIKO SU EFIKASNI APOLIPOPROTEINI ApoB I ApoA-I KOD PACIJENATA SA AKUTNIM KORONARNIM SINDROMIMA

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Summary: Acute coronary syndromes are the leading cause of hospitalization and death. Results from recent studies suggest that apolipoprotein measurement and apoB:apoA-I are superior to traditional lipids in the estimation of coronary risk. We compared apolipoprotein concentrations and apoB:apoA-I with traditional lipid measures and atherogenic indices in patients diagnosed with acute coronary syndromes (ACS) within 6 hrs from the onset of chest pain. A study group consisted of 227 patients diagnosed with ACS (STEMI=60, NSTEMI=66 and UA=105). Clinically healthy volunteers (n=85) served as controls. Measurements of cardiac TnI, lipid profile, hsCRP, apolipoprotein A-I and apoB100 were performed and apoB:apoA-I, TC-HDL-C, LDL-C:HDL-C ratios were calculated. Patients had increased LDL-C (>3.0 mmol/L) and non-HDL-C (>3.4 mmol/L). Triglycerides were below the cut-off value, but patients had significantly higher TG concentrations and lower HDL-C compared to controls ($p<0.001$). Apo B and apoA-I concentration in patients remained within the accepted range. Atherogenic indices TC:HDL-C, LDL-C:HDL-C and apoB:apoA-I were significantly increased in patients. ApoB:apoA-I ratio in ACS males was within low risk whereas in females corresponded to medium risk. ApoB:apoA-I and LDL-C:HDL-C ratios were of good diagnostic utility for discrimination between patients and controls (AUC 0.71 and 0.79; respectively). ApoB:apoA-I and LDL-C:HDL-C were of very good diagnostic utility for discrimination between STEMI patients and controls (AUC 0.80 and 0.84). We could not show the superiority of apoB:apoA-I over LDL-C:HDL-C as the discri-

Kratak sadržaj: Akutni koronarni sindrom predstavlja vodeći uzrok hospitalizacija i smrti. Rezultati skorašnjih studija pokazuju da se u proceni koronarnog rizika bolje pokazalo merenje apolipoproteina i apoB:apoA-I nego tradicionalnih lipida. Uporedili smo koncentracije apolipoproteina i apoB:apoA-I sa tradicionalnim lipidskim merama i aterogenim indeksima kod pacijenata sa dijagnozom akutnog koronarnog sindroma (ACS) u roku od 6 sati od nastanka bola u grudima. Proučavanu grupu činilo je 227 pacijenata sa dijagnozom ACS (STEMI=60, NSTEMI=66 i nestabilna angina pektoris=105). Klinički zdravi dobrovoljci (n=85) služili su kao kontrola. Izmereni su srčani TnI, lipidski profil, hsCRP, apolipoprotein A-I i apoB100 i izračunati odnosi apoB:apoA-I, TC-HDL-C, LDL-C:HDL-C. Pacijenti su imali povišen LDL-C (>3,0 mmol/L) i ne-HDL-C (>3,4 mmol/L). Trigliceridi su bili ispod cut-off vrednosti, ali pacijenti su imali značajno više koncentracije TG i niži HDL-C u poređenju sa kontrolama ($p<0,001$). Koncentracija apo B i apoA-I kod pacijenata ostala je u okviru prihvaćenog opsega. Aterogeni indeksi TC:HDL-C, LDL-C:HDL-C i apoB:apoA-I bili su značajno viši kod pacijenata. Odnos apoB:apoA-I kod muškaraca sa ACS ukazivao je na nizak rizik, dok je kod žena odgovarao srednjem riziku. Odnosi apoB:apoA-I i LDL-C:HDL-C bili su dijagnostički korisni za razlikovanje pacijenata od kontrola (AUC 0,71 i 0,79). ApoB:apoA-I i LDL-C:HDL-C bili su veoma dijagnostički korisni za diskriminaciju između pacijenata sa STEMI i kontrola (AUC 0,80 i 0,84). Nismo uspeli da pokažemo superiornost apoB-

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Abbreviations: STEMI – ST-elevation myocardial infarction, NSTEMI – non-ST-elevation myocardial infarction, UA – unstable angina pectoris

mination power of both was almost identical. Determination of apolipoproteins should not be recommended for routine clinical use, however, incorporating apoB and apoB:apoA-I into risk assessment could provide additional important information on cardiovascular risk.

Keywords: acute coronary syndromes, apolipoproteins, cardiovascular risk

apoA-I u odnosu na LDL-C:HDL-C pošto je njihova diskriminatorna moć gotovo identična. Određivanje apolipoproteina ne bi trebalo preporučivati za rutinsku kliničku upotrebu, međutim, uključivanje apoB i apoB:apoA-I u procenu rizika moglo bi obezbediti dodatne važne informacije o kardiovaskularnom riziku.

Ključne reči: akutni koronarni sindromi, apolipoproteini, kardiovaskularni rizik

Introduction

According to data published in the National Registry of Acute Coronary Syndromes (PL-ACS) every year in Poland 140.000 subjects are diagnosed with acute coronary syndromes (ACS) (1). Acute coronary syndromes are a group of disorders developing as a consequence of atherosclerosis and characterized by changes in the coronary circulation, whose common feature is the significant reduction or cessation of blood flow in the coronary arteries. The most common cause of circulatory disorders is a blood clot formed at the rupture of atherosclerotic plaque. Novel cardiac biomarkers are used to identify patients with ACS even when there is no evidence of cardiomyocyte damage (myeloperoxidase, ischemia-modified albumin, heart-fatty acid binding protein). Similarly, novel biomarkers are assessed that may be regarded as risk discriminators of cardiovascular disease (CVD) with a predictive value for future events. Apolipoprotein B (apo B) and apolipoprotein A-I (apo A-I), either separately or together as a calculated apoB:apoA-I ratio, may predict CVD risk more accurately than traditional lipid profile measurement.

Each proatherogenic lipoprotein fraction: VLDL, IDL, and LDL contains one apo B molecule per particle, therefore the serum concentration of apo B reflects the total number of atherogenic particles (2). HDL is the only antiatherogenic lipoprotein and its major structural protein is apo A-I. This protein produced both in the liver and intestine is involved in reverse cholesterol transport carrying excess cholesterol from peripheral tissues back to the liver for excretion (3).

In spite of the availability of standardized commercial assays, apo B and/or apoA-I are not yet widely measured in routine medical laboratory practice. Data suggest that measurement of apo B potentially could provide several advantages over the conventional measurement of LDL-cholesterol (LDL-C) and non-HDL-C as a cardiovascular disease risk index. Apo B can be measured directly and with a high accuracy and precision in the nonfasting state (4). The reliability and reproducibility of apo B assays are comparable to those expected for non-HDL-C, a measure of all the cholesterol in atherogenic lipoproteins (5).

The optimal value for LDL-cholesterol (LDL-C) is <2.6 mmol/L, for non-HDL-C it is <3.4 mmol/L and the optimal apo B concentration is <0.9 g/L (6). Results above these values indicate an increased risk of CVD including acute coronary syndromes. Even the most accurate determinations of LDL-C or non-HDL-C, obtained after calculation of other parameters, do not fully reflect the proatherogenic impact of apo B containing lipoproteins. Studies showed that in subjects with normal or slightly increased concentrations of LDL-C, apo B is a better indicator of CVD risk. This comes from the fact that even with a slightly elevated concentration of LDL-C in the blood, with concomittant hypertriglyceridemia and low HDL-C, very often an increase of small dense LDL particles occurs (7). Small dense LDL have up to 25% lower cholesterol content per one apo B molecule than large LDL particles (8). Cardiovascular risk is more directly related to the number and size of atherogenic particles than to their cholesterol concentration (4, 7, 9).

The concentration of apo Al in the circulation is approximately 1–1.3 g/L, and the majority of this protein (99%) is a part of HDL. Concentration of apo A-I below 1.2 g/L is related to greater risk of CVD (10). The cholesterol content of HDL particles is influenced by blood triglyceride concentration and in, general, hypertriglyceridemia is associated with low HDL-C and low apo A-I values (11, 12). The most useful as a predictor of CVD risk seems to be the calculated apoB:apoA-I ratio (13). Previous reports have shown that an apoB:apoA-I ratio of <0.7 and <0.6 for men and women respectively is associated with low risk for cardiovascular disease. ApoB:apoA-I corresponds to the relationship between proatherogenic apo B-containing lipoproteins and anti-atherogenic HDL fraction (13). The advantage of calculating this ratio is that the concentrations of both apolipoproteins are not influenced by a nonfasting state and during daytime. In addition, with regard to the tests performed after acute coronary syndromes have occurred, it does not matter how much time has elapsed since the blood collection. This is a valuable piece of information, because in patients suspected with ACS the credibility of lipid measurement is questioned if the blood was collected within 24 hours after the incident.

Results from recent studies suggested that the serum concentration of apo B and apo A-I as well as the apoB:apoA-I ratio are related to the occurrence of ACS in different ethnic populations (8). We aimed to compare apolipoprotein concentrations and the apoB:apoA-I ratio with the traditional lipid measures in patients diagnosed with acute coronary syndromes.

Materials and Methods

A study group consisted of 103 women (aged 69±10 years) and 146 men (aged 61±13 years) who were admitted to the Department of Cardiology and Internal Medicine of the University Hospital between September 2008 and March 2009. All patients presented with chest pain initiating within 6 hours before the hospital admission. Electrocardiography examination was performed on admission and thereafter if clinically indicated. Echocardiography, stress tests and cardiac catheterization were performed if needed. Altogether 227 patients were finally diagnosed with ACS and 22 patients as having other heart disease or unspecified chest pain. ACS patients were subsequently definitely diagnosed with unstable angina (UA n=105), non-ST-elevation myocardial infarction (NSTEMI n=66) or ST-elevation myocardial infarction (STEMI n=60). Patients with heart failure, pulmonary embolism, chronic obstructive pulmonary disease, renal insufficiency, myocardial infarction within 6 weeks preceding the enrolment were excluded from the trial.

Clinically healthy volunteers (34 females, aged 54±4 years and 51 males, aged 50±7 years) with no evidence of present renal, metabolic or inflammatory disease, heart failure and recent myocardial infarction served as controls. Hypertension was diagnosed if systolic blood pressure exceeded 140 mmHg and/or diastolic blood pressure was above 90 mmHg, and dyslipidaemia if even one of the lipid profile components was above/under the following values: total cholesterol (TC) >4.9 mmol/L, triglycerides (TG) >1.7 mmol/L, LDL-C>3.0 mmol/L, HDL-cholesterol (HDL-C) <1.3/<1.0 mmol/L females/males according to ESH/ESC recommendations. Non-HDL-C over 3.4 mmol/L was accepted as elevated. Among subjects in the control group, 30% had slightly elevated TC and/or LDL-C and 5% had decreased HDL-C.

The study protocol was approved by the Bioethics Committee at Nicolaus Copernicus University in Torun Collegium Medicum in Bydgoszcz and written informed consent has been obtained from all patients.

Venous blood samples were collected from patients on hospital admission within 6 hours of the chest pain onset. From controls fasting venous blood samples were collected in the morning. Serum was assayed on admission for cTnI, lipid parameters, glucose, hsCRP and BNP (Architect ci8200, Abbott Diagnostics). LDL-C and non-HDL-C were calculated. Any increase of cTnI above 0.032 ng/mL (the 99th percentile for the healthy population measured with 10% CV) was considered a positive result. Serum apoA-I and apo B100 concentrations were measured in samples stored frozen at –80 °C not longer than 6 months (Abbott ARCHITECT ci8200) and the ratio of apoB:apoA-I was calculated. ApoB concentration >0.9 g/L was accepted as elevated, whereas apoA-I <1.2 g/L was accepted as decreased. ApoB:apoAI ratio <0.3/0.4 and LDL-C:HDL-C <2.3/<2.9 for females/males and TC:HDL-C <4/<5 for females /males were accepted as optimal. According to Walldius et al. (12) apoB:apoA-I ratio within 0.3–0.6 or 0.4–0.7 for females/males was considered as low risk; 0.6–0.8 or 0.7–0.9 was considered as medium risk and >0.8/>0.9 for females/males as high risk of myocardial infarction.

Statistical methods

Data were presented as medians and 25th and 75th percentiles. U-Mann-Whitney test and ANOVA were used to compare differences. ROC analysis was performed and AUC were calculated. Statistical analysis was performed using Statistica 8.0 for Windows.

Results

Tables Ia, b show the general characteristics of the study groups. The most distinctive feature of both females and males with ACS was increased LDL-C

Table Ia Characteristics of the study groups (females).

Parameter	ACS patients (Females n=94)	Control group (Females n=34)
Age (years)	68.8±9.9	54±3[a]
TC (mmol/L)	5.03 (4.23–6.0)	4.72 (4.46–5.0)[b]
HDL-C (mmol/L)	1.16 (1.0–1.42)	1.6 (1.44–1.78)[a]
non-HDL-C	3.95 (3.09–4.54)	3.09 (2.71–3.38)[a]
TC:HDL-C	4.3 (3.5–4.8)	2.9 (2.6–3.2)[a]
LDL-C (mmol/L)	3.2 (2.53–3.95)	2.63 (2.42–2.97)[b]
LDL-C:HDL-C	2.63 (1.99–3.29)	1.62 (1.41–1.85)[a]
TG (mmol/L)	1.29 (1.0–1.75)	0.84 (0.69–1.09)[a]
apoA-I (g/L)	1.32 (1.14–1.48)	1.58 (1.41–1.66)[a]
apoB (g/L)	0.8 (0.64–0.97)	0.72 (0.62–0.80)
apoB:apoA-I	0.62 (0.5–0.75)	0.47 (0.42–0.53)[a]

a: p<0.001 ACS and control group; b: p<0.05 ACS and control group

Table Ib Characteristics of the study groups (males).

Parameter	ACS patients (Males n=133)	Control group (Males n=51)
Age (years)	61.4±13.3	50.2±7.1[b]
TC (mmol/L)	4.85 (4.02–5.98)	4.54 (4.02–4.95)[b]
HDL-C (mmol/L)	1.0 (0.9–1.21)	1.34 (1.13–1.47)[a]
non-HDL-C	3.82 (2.99–4.72)	3.2 (2.6–3.53)[a]
TC:HDL-C	4.5 (4.0–5.7)	3.5 (2.69–3.8)[a]
LDL-C (mmol/L)	3.15 (2.29–3.87)	2.71 (2.14–3.15)[b]
LDL-C:HDL-C	2.86 (2.43–3.78)	2.1 (1.6–2.5)[a]
TG (mmol/L)	1.39 (1.02–2.07)	1.16 (0.71–1.32)[a]
apoA-I (g/L)	1.22 (1.07–1.37)	1.25 (0.98–1.43)[a]
apoB (g/L)	0.81 (0.67–1.02)	0.67 (0.54–0.85)[a]
apoB:apoA-I	0.68 (0.55–0.84)	0.55 (0.46–0.66)[a]

a: $p<0.001$ ACS and control group; b: $p<0.05$ ACS and control group

(>3.0 mmol/L) and non-HDL-C (>3.4 mmol/L). Although median concentration of triglycerides was found to be below the cut-off value, patients diagnosed with ACS had significantly higher TG concentration and lower HDL-C compared to controls ($p<0.001$). Median apo B concentration in ACS patients remained within the accepted optimal range, but in a group of males was significantly higher than in controls. Similarly, median apo A-I concentration in ACS patients was within the optimal range but in females was lower than in respective controls ($p<0.001$).

Atherogenic indices TC:HDL-C, LDL-C:HDL-C and apoB:apoA-I were significantly increased in patients with ACS compared to controls. Median TC:HDL-C and LDL-C:HDL-C in males diagnosed with ACS were found to be close to the cut-off value, but they were over the cut-off in females. Increased CVD risk in females, reflected by TC:HDL-C >4 and LDL-C:HDL-C >2.3, was found in 61% and 64.5%, respectively, whereas in males a ratio TC:HDL-C >5 and LDL-C:HDL-C >2.9 was observed in 42% and 50.3%, respectively.

Median apoB:apoA-I ratio in ACS males was in the range of low risk whereas in females this ratio corresponded to medium risk. In females diagnosed with ACS increased CVD risk reflected by an apoB:apoA-I ratio >0.6 was found in 58% and in males an apoB:apoA-I ratio >0.7 was observed in 50%.

In ACS patients better correlation was observed for non-HDL-C and apoB concentration ($r= 0.74$ in females and $r=0.85$ in males; $p<0.001$) than for LDL-C and apo B, whereas the correlation of apoB:apoA-I ratio with both TC:HDL-C or LDL-C:HDL-C was similar ($r=0.74$ in females and $r= 0.84$ in males; $p<0.001$).

ROC analysis was performed for all atherogenic indices, LDL-C, HDL-C, non-HDL-C, apo B and apo A-I, to discriminate between patients with ACS diagnosis and controls and the best discriminators were chosen. Both the calculated apoB:apoA-I and LDL-C: HDL-C ratios were of good diagnostic utility for the discrimination between patients diagnosed with ACS and controls (areas under the ROC curve–AUC were 0.71 and 0.79; respectively) (*Table II*).

Table II Diagnostic utility of selected parameters measured in the study groups.

	Parameter	AUC
ACS patients vs controls	apoB:apoA-I	0.71
	LDL-C:HDL-C	0.79
	apoB	0.66
	non-HDL-C	0.72
	LDL-C	0.66
ACS (STEMI) patients vs controls	apoB:apoA-I	0.80
	LDL-C:HDL-C	0.84
	non-HDL-C	0.79
	apoB	0.75
	LDL-C	0.74

Among others, non-HDL-C was a slightly better discriminator than apo B alone (AUC 0.72 and 0.66; respectively).

Table III shows the characteristics of the ACS group according to the clinical diagnosis. The differences between most measured parameters, in ACS patients with different clinical diagnosis, did not reach statistical significance, excluding the LDL-C concentration and apoB:apoA-I value that were the highest in patients with the diagnosis of STEMI ($p<0.05$). Patients with STEMI had also the highest median apoB concentration. Furthermore, in 46% of patients with STEMI the highest apoB:apoAI values (top tertile), from 0.65–1.29 in females and 0.8–1.45 in males, were observed, while in 30–40% of those with UA and NSTEMI the lowest values (in the lowest tertile)

Table III Characteristics of the ACS patients according to the clinical diagnosis.

Parameter	STEMI (n=60)	NSTEMI (n=66)	UA (n=105)
Age (years)	64.4±12.5	67.3±14	63.1±11.1
TC (mmol/L)	5.21 (4.46–6.24)	4.82 (4.12–5.75)	4.82 (3.92–5.98)
HDL-C (mmol/L)	1.11 (0.93–1.31)	1.13 (0.93–1.31)	1.08 (0.93–1.31)
n-HDL-C (mmol/L)	4.02 (3.46–4.87)	3.92 (2.89–4.64)	3.74 (2.94–4.56)
TC:HDL-C	4.5 (3.8–5.4)	4.4 (3.3–5.4)	4.4 (3.8–5.4)
LDL-C (mmol/L)	3.58 (2.5–4.13)	3.2 (2.45–3.79)	2.84 (2.24–3.82)*
LDL-C:HDL-C	2.95 (2.48–3.74)	2.94 (1.9–3.63)	2.68 (2.1–3.36)
TG (mmol/L)	1.21 (0.83–1.63)	1.3 (1.0–2.02)	1.4 (1.07–2.08)
apoAI (g/L)	1.25 (1.11–1.41)	1.25 (1.08–1.42)	1.23 (1.10–1.41)
apoB (g/L)	0.86 (0.73–1.08)	0.80 (0.64–0.93)	0.76 (0.63–0.95)
apoB:apoAI	0.71 (0.6–0.86)	0.64 (0.46–0.78)	0.63 (0.5–0.8)*

Statistically significant differences * $p < 0.05$ (ANOVA)

from 0.29–0.51 and 0.27–0.60 for females and males, respectively, were found (results not shown). This was not observed for other atherogenic indexes.

The calculated apoB:apoA-I and LDL-C:HDL-C ratios were of very good diagnostic utility for the discrimination between patients and controls only in the STEMI group (AUC were 0.80 and 0.84; respectively) (*Table II*). Among others, non-HDL-C, apoB and LDL-C had a good discrimination power.

Discussion

In this study, performed in patients presenting with chest pain and further diagnosed with ACS, we aimed to evaluate whether apolipoproteins B and A-I and the apoB:apoA-I ratio perform better than traditional lipids and atherogenic indices in the assessment of risk associated with cardiovascular incidents. Some previous studies have shown that the higher the value of apoB:apoA-I, the higher the risk of incident cardiovascular events (13, 14). We have shown in patients with diagnosed ACS that the apoB:apoA-I ratio was of good diagnostic utility for the discrimination between ACS cases and control subjects (AUC=0.71) and even very good to distinguish STEMI cases which are at the greatest risk (AUC=0.80). However, we could not show the superiority of this ratio over the calculated LDL-C:HDL-C as the discrimination power of both was almost identical. This is further confirmed by the comparison of estimated CVD risk in ACS patients with the use of apoB:apoA-I ratio and the calculated atherogenic indices TC:HDL-C and LDL-C:HDL-C. The percentage of patients with increased CVD risk was almost the same in females and in males irrespective of the ratio used.

Considering the results of our study, only LDL-C and non-HDL-C concentrations in ACS patients were elevated over the accepted cut-off values, whereas the other measured parameters, even though higher or lower (HDL-C, apoA-I) compared to controls, remained within the accepted optimal range. Patients diagnosed with ACS had, in general, moderately higher TG concentrations and decreased HDL-C compared to controls, which allow to assume the occurrence of small dense LDL particles to a relatively small extent. In fact, an elevated apoB concentration over 0.9 g/L in our group of ACS patients was observed only in 33.6%, distributed equally among females and males. It was reported earlier that apoB is more closely associated with metabolic syndrome, hyperinsulinemia and insulin-resistance than the LDL-C concentration (15). In our ACS patients the frequency of diabetes mellitus was 50% and the main clinical feature was hypertension (74%) which may probably explain the relatively low occurrence of elevated apoB in this setting.

It has been demonstrated in one of the first AMORIS studies, that the coronary risk and mortality due to coronary heart disease are associated with high apoB and higher values of apoB:apoA-I, and that this relationship is stronger than that for LDL-C (13, 16). Other subsequent studies, including EPIC-Norfolk study, ULSAM and the MONICA/Cora confirmed that the apoB:apoAI ratio is a useful index of both nonfatal and fatal myocardial infarction (MI) (13). Furthermore, the INTERHEART study showed that the ratio of apoB to apoA-I was not only the strongest risk factor in predicting MI, but was also the most prevalent risk factor of all risk factors independent of age, sex and ethnicity (8). Taking into account the differences between the ACS groups in our study, according to clinical diagnosis, the highest apoB:apoAI ratio was observed predominantly in STEMI patients. On the contrary, the lowest values of the ratio were found predominantly among patients with UA and NSTEMI. From a clinical point of view this is confirmed by the results of recently published studies

(17, 18). Iwahashi et al. (18) explored the impact of apoB:apoAI on the damage to cardiac function after a first ST-elevation myocardial infarction. A significant relationship between the apoB:apoAI ratio and echocardiographical parameters was observed, however apolipoproteins alone and the conventional lipid parameters did not show such associations. Based on the results of this study it was concluded that the value of apoB:apoAI ratio in ACS patients on admission could predict the elevation of left ventricular filling pressure 2 weeks after a first STEMI onset. These results might explain why the higher values of the apoB:apoAI ratio were frequently followed by fatal myocardial infarction (18). Thus the determination of apoB:apoAI on admission to the hospital can distinguish the patients at greatest risk.

The superiority of apolipoprotein B, and especially the apoB:apoA-I ratio in patients with the highest cardiometabolic risk, meaning known CVD or diabetes and two additional major risk factors such as smoking, hypertension, or family history of premature coronary artery disease, for assessing risk of future events and in the secondary prevention in ACS patients seems to be indisputable. On the basis of the data from the present study we cannot conclude that the determination of apolipoproteins should be recommended for routine clinical use, however we may confirm that incorporating apoB and in particular apoB:apoA-I ratio into risk assessment could provide additional important information on cardiovascular risk.

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Conflict of interest statement

The authors stated that there is no conflict of interest regarding the publication of this article.

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